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Successful treatment with imatinib after nilotinib and ipilimumab in a c-kit-mutated advanced melanoma patient: a case report

Murer, Carla ; Kränzlin-Stieger, Pascale ; French, Lars E ; Dummer, Reinhard ; Goldinger, Simone M

Abstract: Treatment of melanoma remains a challenge in advanced disease. Recently, the molecular differentiation in BRAF-mutated, NRAS-mutated and c-kit-mutated melanomas led to new treatment strategies. Different trials show that imatinib or nilotinib lead to meaningful responses in c-kit-mutated melanoma patients. There are little published data on sequential inhibition using these two drugs in melanoma. We describe the sequential use of imatinib after nilotinib in a c-kit-mutated melanoma patient, who progressed on interferon, Allovectin, dacarbazine, nilotinib and ipilimumab, and was finally treated with the c-kit inhibitor imatinib. From July 2011 to September 2011, the patient received ipilimumab (four doses with 3 mg/kg). Clinical assessment after immunotherapy showed disease progression. Therefore, a treatment change to imatinib 800 mg daily was made from February 2012 to May 2013. Under this treatment, the patient showed a partial response as per the RECIST criteria. The present lesions continued responding (computed tomography scans: May 2012-March 2013). Unfortunately, in October 2012, new brain metastases developed. Nevertheless, the use of c-kit inhibitors in c-kit-mutated melanoma patients seems to be a promising treatment option. Furthermore, a delayed response to ipilimumab after 6 months could also have led to or supported the partial response in this case. However, when two biologically similar compounds are administered in a melanoma patient and the tumour mass shows progressive disease upon administration of the first agent, an additional progression with no effect may be expected when the second one is used. This case shows, in contrast, that the use of imatinib after progression upon nilotinib can be beneficial.

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Successful treatment with imatinib after nilotinib and ipilimumab in a c-kit-mutated advanced melanoma patient: a case report

Carla Murer, Pascale Kränzlin-Stieger, Lars E. French, Reinhard Dummer and Simone M. Goldinger

Treatment of melanoma remains a challenge in advanced disease. Recently, the molecular differentiation in BRAF-mutated, NRAS-mutated and c-kit-mutated melanomas led to new treatment strategies. Different trials show that imatinib or nilotinib lead to meaningful responses in c-kit-mutated melanoma patients. There are little published data on sequential inhibition using these two drugs in melanoma. We describe the sequential use of imatinib after nilotinib in a c-kit-mutated melanoma patient, who progressed on interferon, Allovectin, dacarbazine, nilotinib and ipilimumab, and was finally treated with the c-kit inhibitor imatinib. From July 2011 to September 2011, the patient received ipilimumab (four doses with 3 mg/kg). Clinical assessment after immunotherapy showed disease progression. Therefore, a treatment change to imatinib 800 mg daily was made from February 2012 to May 2013. Under this treatment, the patient showed a partial response as per the RECIST criteria. The present lesions continued responding (computed tomography scans: May 2012–March 2013). Unfortunately, in October 2012, new brain metastases developed. Nevertheless, the use of c-kit inhibitors in c-kit-mutated melanoma patients seems to be a promising

treatment option. Furthermore, a delayed response to ipilimumab after 6 months could also have led to or supported the partial response in this case. However, when two biologically similar compounds are administered in a melanoma patient and the tumour mass shows progressive disease upon administration of the first agent, an additional progression with no effect may be expected when the second one is used. This case shows, in contrast, that the use of imatinib after progression upon nilotinib can be beneficial. *Melanoma Res* 27:396–398 Copyright © 2017 Wolters Kluwer Health, Inc. All rights reserved.

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Keywords: c-kit mutation, imatinib, ipilimumab, kinase- inhibitors, melanoma treatment, nilotinib

Department of Dermatology, University Hospital Zurich, Zurich, Switzerland

Correspondence to Carla Murer, MD, Department of Dermatology, University Hospital of Zurich, Gloriastrasse 31, CH-8091 Zurich, Switzerland
Tel: +41 44 255 11 11 25 07; fax: +41 44 255 45 49;
e-mail: carla.murer@usz.ch

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Introduction

The differentiation of melanoma in BRAF-mutated, NRAS-mutated and c-kit-mutated melanomas recently led to new treatment perspectives and strategies [1,2]. Kit is expressed in up to 3% of all melanomas [3] and the c-kit mutation is present in about 40% of mucosal and in 5% of acral melanomas [4]. Mucosal vulvovaginal melanomas have the highest frequency of these mutations [5,6]. C-kit inhibitors, such as imatinib and nilotinib, can target c-kit mutations [7]. Hodi *et al.* [7] reported that imatinib (400 mg administered once or twice daily) can be effective in c-kit-mutated melanoma. Moreover, Tran *et al.* [3] suggest that the second-generation tyrosine kinase inhibitor nilotinib is a promising agent in the treatment of metastatic melanoma harbouring the kit mutation. Several phase II clinical trials are ongoing to further investigate its efficacy.

Only little data on the sequential inhibition with these two drugs in advanced melanoma are available so far [8]. Here, we describe the sequential use of imatinib after nilotinib in a patient with advanced c-kit-mutated melanoma.

Patients and methods

A 56-year-old female patient with an ulcerated acrolentiginous melanoma with a Breslow tumour thickness of 2 mm on the lateral nail wall on the dig I of the right foot underwent primary excision, followed by a wide excision. Because of a local recurrence 1 year later, she was referred to the University Hospital of Zurich, where surgical revision of the local satellites and the sentinel lymph node biopsy not carried out previously were performed. Because of the histological evidence of a lymph node micrometastasis (1/3), lymph node dissection and an adjuvant treatment with pegylated interferon (100 µg subcutaneously weekly) were implemented from September 2009 to January 2010 (Rozati, 2013 #3380). The mutation analysis detected a c-kit mutation on exon 13 (K642F).

Upon progression with new skin metastasis on the right leg, the patient was included in a clinical phase III trial (registered at clinicaltrials.gov, NCT01028222) and was treated intralesionally with 2 mg allovectin-7, a sterile bicistronic plasmid DNA encoding the human major histocompatibility complex class I HLA-B7 protein and

β_2 -microglobulin protein that was injected into a single lesion weekly for 6 consecutive weeks and repeated every 8 weeks [9]. After documented progression 4 months later, the patient was included in another randomized, phase II, open-label, multicentre, two-arm study comparing the efficacy of Tasigna (nilotinib) (Novartis Pharma Schweiz AG, Rotkreuz, Switzerland) versus dacarbazine (DTIC) in c-kit-mutated melanoma patients. First, the patient was treated with DTIC 850 mg/m² every 3 weeks for 12 weeks. Then, upon crossover, the patient received nilotinib 400 mg twice daily according to the protocol for 6 months from January to June 2011. Dose reduction to 200 mg once daily for 5 weeks and dose interruption for 1 week were necessary because of increases in lipase and amylase. New lung metastases were then detected and the patient was excluded from the trial because of progressive disease.

Thereafter, the patient was treated with four infusions of ipilimumab intravenously 3 mg/kg every 3 weeks. This was the only checkpoint inhibitor available at that time in Switzerland. The clinical assessment of the right leg after immunotherapy again showed a clear disease progression. As this young female patient with c-kit-mutated melanoma progressed upon interferon, Allovectin (Vical Incorporated, San Diego, California, USA), DTIC, nilotinib and anti-CTLA-4 treatment, we decided on the first-generation tyrosine kinase inhibitor Glivec (imatinib) (Novartis Pharma Schweiz AG) as compassionate use. The patient was treated with imatinib 800 mg orally daily, showing a partial response as per the RECIST criteria. The present lesions continued responding (computed tomography scans May 2012 to March 2013). Certainly, also a delayed response to ipilimumab after 6 months could have led to or supported this response. Unfortunately, in October 2012, new brain metastases developed.

They were simultaneously treated with whole-brain irradiation with a total of 30 (3×10) Gy and steroids (dexamethasone, initially 12 mg, then 4 mg daily). With this additional treatment, the disease was stabilized for another 6 months. The patient eventually died in May 2013 after epileptic seizures in March 2013 and April 2013.

Discussion

We report on a 56-year-old female patient who was initially treated for 17 weeks with the c-kit inhibitor nilotinib and after several treatment failures (interferon, Allovectin, DTIC, nilotinib and ipilimumab) responded to imatinib for 68 weeks until she died in May 2013. Although the patient experienced adverse events under the treatment with nilotinib that required dose reduction, the treatment with imatinib was tolerated very well. After 36 weeks of treatment, new brain metastases developed. They could be controlled for 32 weeks using steroids for detumescence and whole-brain irradiation. Development of brain metastases during the treatment with imatinib is

a typical feature due to the inability for imatinib to pass through the brain–blood barrier [10].

However, the use of tyrosine kinase inhibitors in c-kit-mutated melanoma patients seems to be a promising treatment option [8,11,12]. More precisely, in a phase II clinical trial with 43 c-kit-mutated melanoma patients treated with imatinib administered 400 mg/day, the median progression-free survival was 3.5 months and the 6-month progression-free survival rate was 36.6%. One-year overall survival rate was 51% and the overall response rate was 23.3% [13]. Complete responses in metastatic c-kit-mutated melanoma with imatinib were also reported [8,14,15].

In an open-label, single-centre trial in Korea, nine patients (3/9 with kit mutation in exon 11 and 6/9 with kit amplification) were treated with nilotinib 800 mg/day. Two of the treated patients, both with the kit mutation, achieved a partial response and five patients achieved stable disease, indicating the potential of treatment [16]. Larger clinical trials with nilotinib are ongoing to further determine its efficacy in metastatic melanoma. So far, successful nilotinib treatment after imatinib progression has been published in a small melanoma cohort [17] and in chronic myelogenous leukaemia (CML) [12,18,19]. Our case shows that the inverse administration that is, the use of imatinib after progression upon nilotinib and ipilimumab in melanoma can lead to good clinical and radiological results. This is in agreement with published data on nilotinib-resistant and imatinib-resistant cell lines that provide a rationale for treating patients with melanoma progressing on imatinib or nilotinib with alternative tyrosine kinase inhibitors *in vitro* [8]. Furthermore, Guo *et al.* [13] describe the best response rates to imatinib in melanomas harbouring the c-kit mutation in exon 11 and 13, as was the case in our patient.

Resistance to imatinib and nilotinib has been reported frequently [8,11,12,18]. Development of therapeutic resistance to imatinib might be caused by NRAS mutations and kit copy number [7]. Camgoz *et al.* [18] studied nilotinib-resistant cells and described an upregulation of antiapoptotic BCR/ABL, GCS and SK-1 genes and the MRP1 transporter gene and downregulation of apoptotic Bax and CerS1 genes. This suggests that the development of resistance mechanisms to nilotinib and imatinib might be different and could explain why our patient responded to imatinib after progression upon nilotinib. Another possible explanation is the intermittent administration of the two tyrosine kinase inhibitors to reduce drug resistance development as Das Thakur *et al.* [20] reported for vemurafenib. Furthermore, our patient received ipilimumab between the two treatments. Upregulation of T cell activity might play a role in generating better results of further targeted therapies. This is supported in other case reports, in agreement with Balakan *et al.* [21], where the selective BRAF inhibitor

vemurafenib was administered after ipilimumab in a patient with brain metastases with good response; we believe that the sequential administration may have contributed towards the good imatinib outcome. In addition, similar findings were observed in a large phase III trial for NRAS mutant patients treated with MEK inhibitors [22]. The administration of ipilimumab with a subsequent increase in the activity of the immune system could play a role in the stabilization of the disease. A further explanation in this specific case for the better and more durable response to imatinib than to nilotinib could be the better side-effect profile [13]. This can lead to a better dose and treatment management and a higher plasma level. In our patient, the dose of nilotinib had to be reduced because of adverse events and might have led to reduced efficacy. In addition, the presence of a higher tumour load with progressive metastasis could implicate an increased concentration of c-kit-mutated tumour cells, where the use of the second c-kit inhibitor might lead to better results.

In CML patients, nilotinib shows better response rates compared with imatinib. Moreover, dasatinib, another second-generation tyrosine kinase inhibitor, shows good efficacy when used upon progression after nilotinib and imatinib in CML patients [12]. However, preliminary data show minimal efficacy in unselected melanomas and poor tolerance [19,23]. It would be interesting to learn more about possible new treatment strategies in c-kit-mutated melanoma. This is a case report and it is therefore not possible to draw general conclusions. Furthermore, data were not collected prospectively and were not standardized as in a clinical trial setting. However, the incidence of this type of melanoma is low and this renders the realization of a large clinical trial difficult.

In this case, we observed a clear benefit of imatinib after the administration of nilotinib and ipilimumab in c-kit-mutated melanoma. Certainly, we have to underline that a delayed response to ipilimumab after 6 months could have also led to or supported the partial response in this case. Yet, we believe that the therapies discussed could be a good treatment strategy in c-kit-mutated melanoma and therefore plan to treat more patients to support the observed trend. The approach outlined in this case report should be assessed in a larger cohort and should be studied further.

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Conflicts of interest

R.D. declares research funding from Novartis, Bristol Meyers Squibb, Roche, Glaxo Smith Kline and has consultant and advisory board relationships with Novartis, Merck Sharp & Dhome, Roche, Bristol Meyers Squibb, Glaxo Smith Kline and Amgen. S.M.G. declares research funding from the University Hospital of Zurich, received travel grant support from Merck Sharp & Dhome, Roche, Novartis and Bristol Meyers Squibb, and has advisory relationships for Merck Sharp & Dhome,

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